AMENDMENTS TO THE SPECIFICATION:

Please amend this application on page 1, line 1, by inserting the following new paragraph:

This application is the National Stage of International Application No. PCT/EP2005/000906, filed January 31, 2005, which claims benefit of DE 10 2004 004 882.7, filed January 30, 2004, each of which is incorporated herein by reference.

On page 33, please amend the paragraph that begins at line 6 as follows:

In this connection, the probe (4) is preferably to be selected such that the binding of the probe component (8) to the analyte (A1) is more stable than the binding of the probe components (7) and (8) to each other. This can be achieved by the hybrid composed of the probe component (8) and the analyte (A1) comprising more homologous base pairs than the hybrid of the two probe components (7) and (8). As a result, the stability or melting temperature of the hybrid between the probe component (8) and the analyte (A1) is higher than that of the probe (4). Firstly, the probe components (7) and (8) are separated from each other by appropriately raising the temperature and/or in some other way altering the experimental conditions ~~(VB1)~~ (EC1), for example the salt concentration. A further change in the experimental conditions ~~(VB2)~~ (EC2), for example a lowering of the temperature, then leads to the association of the probe component (8) with the analyte (A1) before reassociation of the probe components (7) and (8) can take place since the association stability or the melting

temperature or reassociation temperature of the hybrid of the probe component (8) with the analyte (A1) is higher than that of the probe (4), i.e. of the probe components (7) and (8) with each other. The specificity and sensitivity of such a system is greater than of a system in which the melting temperatures are comparable.

On page 56, please amend the paragraph that begins at line 14 as follows:

Even if other analytes can be detected, particular preference is given to detecting nucleic acids. For example, HIV-1 can be detected using a molecular switch described in c) when 5'-**GCGAGC**CTGGGATTAAATAAAATAGTAAGAATGTATAGC**GCTCGC**-3' (SEQ ID NO: 1) is used as the oligonucleotide. The underlined region corresponds to the sequence which hybridizes with the analyte, i.e. the nucleic acid sequence of HIV-1. The bases in bold are used for the intramolecular hybridization of the probe.

On page 59, please amend the paragraph that begins at line 5 as follows:

Glucose 6-phosphate dehydrogenase (G6PDH) is conjugated to an oligonucleotide having the sequence 5'-gtatctagctatgttgatggtg-3' (SEQ ID NO: 7). The 5'-SH-modified oligonucleotide is coupled using a heterofunctional, non cleavable, water-soluble crosslinker. The crosslinker sulfo-EMCS is used in accordance with Pierce's instructions (product sheet: Pierce Biotechnology, Inc. www.piercenet.com, "Instructions EMCS and Sulfo-EMCS") ~~(name to be given 2003-2004)~~. This conjugation

is preferably effected in the presence of glucose 6-phosphate and/or β-NADH. The above-mentioned sequence is used for detecting bacteriophagelambda DNA (λ).

Please amend the paragraph that begins on page 60, line 33, as follows:

The oligonucleotide 5'-**GCGAGC**gtatctagctatgttgatggtg**GCTCGC**-3' (SEQ ID NO: 2) is, for example, used for detecting bacteriophage DNA. The region written in small letters corresponds to the sequence which hybridizes with the analyte, i.e. the nucleic acid sequence of the bacteriophage DNA. The bases in bold are used for the intramolecular hybridization.

Please amend the paragraph that begins on page 61, line 5, as follows:

The purified molecular switch diaphorase × λ × streptavidin (DLS) is used for detecting bacteriophage DNA as follows. DLS is incubated with samples. The samples comprise purified DNA. An incubation in 5 to 500 mM tris-HCl, pH 6 to 10, in particular, however, in 50 mM tris-HCl, pH 8.6, 50 mM NaCl, is carried out first of all. The temperature is between 4 and 98°C, in particular, however, between 30 and 95°C and preferably about 80°C. After an incubation of from 0.1 to 20 minutes, in particular, however, of between 2 and 10 minutes, preferably of about 5 minutes, the nucleic acids had been converted into single strands. After that, the temperature was lowered down to from 40 to 70°C, in particular, however, to from 50 to 60°C, preferably, however, to about 55°C. When bacteriophage DNA is present, it hybridizes with the molecular

switch probe. If no bacteriophage DNA is present, the intramolecularly hybridized probe is formed once again. The detection reaction is effected, in accordance with Bergmeyer (Bergmeyer 1965), by adding iodonitrotetrazolium chloride (INT), β-NADH and NAD. Other tetrazolium salts, such as neotetrazolium chloride (NT), thiocarbamyl nitro blue tetrazolium chloride (TCNBT), tetra nitro blue tetrazolium chloride (TNBT), nitro blue tetrazolium chloride (NTB), ~~benzothiozolylstyrylphthalhydrozidyltetrazolium~~ benzothiazolylstyrylphthalhydrozidyltetrazolium chloride (BSPT), WST-1, WST-3, WST-4 and, in particular, cyanoditolyltetrazolium chloride (CTC), are used instead of INT where appropriate. The detection is effected by determining absorption of fluorescence in cuvettes or microtiter plates using appropriate spectrophotometers or fluorimeters at the appropriate wavelengths. The change in the signals is measured at a particular time point or over a given time interval and the conversion or the reaction rate is determined in this way. In the presence of bacteriophage DNA, the conversion is increased proportionally depending on the quantity of bacteriophage DNA. The bacteriophage DNA which is bound removes the blocking of the access to the catalytic centre.

Please amend the paragraph that begins on page 62, line 32, as follows:

In one particular embodiment, the hexokinase used in the 3rd exemplary embodiment is employed together with the probe 5'-**GCGAGC**gtatctagctatgttgatggtg**GCTCGC**-3' (SEQ ID NO: 2). In this case, the

molecular switch consequently has the structure hexokinase-5'-**GCGAGC**gtatctagctatgttgatggtg**GCTCGC**-3'-biotin-streptavidin (SEQ ID NO: 2). The following molecular switch is used in addition: glucose 6-phosphate dehydrogenase-5'-**GCGAGC**ctgtacgtgtggcagttgct**GCTCGC**-3'-biotin-streptavidin (SEQ ID NO: 3). The probe belonging to this switch is also used for detecting bacteriophage DNA but in another sequence region. The experimental conditions which are selected are those used in exemplary embodiment 2. However, in this assay, the bacteriophage DNA is detected by two molecular switches. This unexpectedly increased the specificity of the detection. The overall reaction:

D-glucose + ATP-G6PDH → glucose 6-phosphate + ADP

Glucose 6-phosphate + NADPH + H^+-G6PDH → Gluconate 6-phosphate + NAD

can only take place when both binding events are successful. Following Bergmeyer (Bergmeyer 1965), D-glucose, ATP and NADPH are used as the substrates. The oxidation of the NADPH is monitored photometrically or fluorimetrically.

Please amend the paragraph that begins on page 63, line 35, as follows:

In a further exemplary embodiment, G6PDH is conjugated, as detailed in the 1st exemplary embodiment, to the oligonucleotide aptamer 5'SH-TGGTTGGTGTGGTTGGT-3' (SEQ ID NO: 4) for the purpose of binding human alpha-thrombin (thrombin). The purified molecular switch, i.e. ~~G6PDH × thrombin~~ G6PDH-5' - TGGTTGGTGTGGTTGGT-3' - aptamer (SEQ ID NO: 4), is brought into contact with

human alpha-thrombin at between 4 and 70°C, preferably at about 25°C, in about 20 mM tris/HCl, pH 7.4, 140 mM NaCl, 5 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 5% (v/v) glycerol. The binding of the human alpha-thrombin to the oligonucleotide aptamer, and the conformational change in the oligonucleotide aptamer which is thereby induced, lead to a change in the activity of the molecular switch, which change was, in a given concentration range, proportional to the concentration of the analyte, i.e. of the human alpha-thrombin. The activity of the molecular switch is carried out, in accordance with the directions given in the 1st exemplary embodiment, by adding the substrates which are described in that embodiment and following the procedural instructions given.

Please amend the paragraph that begins on page 64, line 21, as follows:

In addition, the abovementioned coupling methods are used to construct a galactose oxidase × 5'-**GCGAGC**gtatctagctatgttgatggtg**GCTCGC**-3' (SEQ ID NO: 2) × biotin/streptavidin switch for detecting bacteriophage DNA. A variety of substrates are employed in the detection reaction, which is carried out in accordance with the descriptions given in Bergmeyer (Bergmeyer 1965) or in Molecular Probes - Fluorescence Microplate Assays (Molecular Probes 1998). The conversion of galactosylated protein is influenced more strongly by the binding of the bacteriophage DNA than is the conversion of galactose. The conversion of the galactose serves as a reference for estimating the overall activity of the system or the change in this activity resulting from the reaction conditions, for example as a result of side reactions and

inactivations. The conversion of the galactosylated protein is the actual indicator for the binding of the bacteriophage DNA. Both values are taken into consideration for optimally determining the concentration of the bacteriophage DNA. The difference or the quotient of the two activities is, for example, used for this purpose.

Please amend the paragraph that begins on page 65, line 10, as follows:

Glucose 6-phosphate dehydrogenase (G6PDH) is conjugated, in accordance with the descriptions given in the 1st exemplary embodiment, to an oligonucleotide having the sequence 3'-**GCGAGC*catag***-5' (SEQ ID NO: 5). However, in this case, the conjugation takes place by way of the 3' end. In order to generate an intermolecularly hybridized probe, hybridization then takes place with 5'-**CGCTCG*gtatc***tagctatgttgatggtg-3' (SEQ ID NO: 6). The hybridization of the intermolecular probe is consequently effected by way of the sequence region which is written in bold. The sequence region which is written in small letters is used for recognizing the bacteriophage DNA. The region which is written in italic is used both for the hybridization of the intermolecular probe and for recognizing the bacteriophage DNA. In particular exemplary embodiments, the oligonucleotide 5'-**CGCTCG*gtatc***tagctatgttgatggtg-3' (SEQ ID NO: 6) is conjugated at its 5' end to biotin and, where appropriate, streptavidin.

Please amend the paragraph that begins on page 67, line 3, as follows:

Glucose 6-phosphate dehydrogenase (G6PDH) is conjugated to an oligonucleotide having the sequence 5'-gtatctagctatgttgatggtg-3' (SEQ ID NO: 7). The coupling of the 5-SH-modified oligonucleotide is effected using a water-soluble crosslinker which carries at least one of the abovedescribed selective components such as ethidium bromide homodimer-1.

Please amend the paragraph that begins on page 68, line 11, as follows:

It is naturally also possible, as mentioned above, to employ systems in which the selective component has a higher affinity for unhybridized nucleic acids, for example single-stranded DNA. In this case, the binding processes, conformational changes and activities of the molecular switches change in a corresponding manner in the absence or presence of an analyte. It is naturally possible for the selective components to be combined with the exemplary embodiments which are described in ~~MA 1250~~ the present specification.

Please insert the attached paper copy of the Sequence Listing before the claims.